IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Linda M. Pacioretty *et al.*
Application No.:	10/699,195
Filing Date:	10/31/2003
Docket Number:	CLANACCR_001NP
Title:	**COMPOSITIONS AND METHODS FOR THE TREATMENT OF HIV-ASSOCIATED FAT MALDISTRIBUTION AND HYPERLIPIDEMIA**
Examiner:	Chong, Young Soo
Art Unit:	1617

CERTIFICATE OF TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service as "EXPRESS MAIL" MAILING LABEL NUMBER EO 953 411 815 US in an envelope addressed to MAIL STOP, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date indicated below.

Date: 10/27/08

John G. Babish

MAIL STOP
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

I, John G. Babish declare as follows:

1. I am Dr. John G. Babish, Chairman, Bionexus, Ltd. I have held this position since June 1997.

2. I have Doctorate and Masters degrees, respectively, in Biochemistry and Chemistry from Cornell University, as well as a Bachelor degree in Biochemistry from The Pennsylvania State University.

3. On the basis of 30 years of training, research publications, grants and experience, I am an expert in the art of molecular biology of pharmaceuticals and xenobiotics. A copy of my Curriculum Vitae is attached as Exhibit A.

4. Additionally, I have served as Senior Pharmacologist in two clinical studies involving the testing of dietary supplements in HIV-positive subjects. In one of these studies, conducted during the filing of the instant application, the objective was to assess the effects of a supplement formulation on lipodystrophy (fat maldistribution) in HIV-positive subjects receiving highly active anti-retroviral treatment (HAART). During the two-year course of this study, I developed an understanding of the clinical presentation of lipodystrophy (fat maldistribution) and hyperlipiedemia associated with anti-retroviral treatment of HIV infection and the response of these metabolic disturbances to dietary supplements.

5. I am co-inventor with Dr. Linda M. Pacioretty on the instant application and I am also a co-inventor on 16 domestic patents and 50 domestic patent applications.

6. I understand that in the course of the Office Action mailed July 29, 2008, the Examiner requested a DECLARATION UNDER 37 CFR 1.132 to compare the claimed subject matter with the closet prior art in order to be effective to rebut a prima facie case of obviousness. I also understand that it is the Applicant's burden to explain any proffered data and establish how any results should be taken to be **unexpected** and *significant*. Additionally, I will compare the claimed invention with prior art that is closer than that applied by the examiner.

7. In this Declaration, I will provide evidence of inoperability of the prior art and unexpected results of our own clinical trials thus demonstrating how the claims of the instant application continue to address a significant and unfulfilled need in the patient population.

7.1. Inoperability of the prior art

7.1.1. **Conjugated linoleic acids (CLA) cause lipodystrophy in mice**. A published mouse study described the loss of adipose tissue, hepatomegaly, the upregulation of TNFα, and development of lipodystrophic diabetes in mice administered CLA in the diet. Seven-week old, female C57/B6 mice were fed a standard laboratory diet supplemented with 1% CLA for four days to eight months [Tsuboyama-Kasaoka, N., Takahashi, M.,

Tanemura, K., Kim, H. J., Tange, T., Okuyama, H., Kasai, M., Ikemoto, S., and Ezaki, O. Conjugated linoleic acid supplementation reduces adipose tissue by apoptosis and develops lipodystrophy in mice. *Diabetes* **2000**, *49*, 1534-42]. The study concludes, "This article reports the first observation that a dietary component causes lipodystrophy and suggests that some agents that decrease fat mass may lead to lipodystrophy."

7.1.2. **A meta-analysis reveals CLA fail to lower blood lipids in normal, human subjects may be harmful to human health and may induce lipodystrophy and insulin resistance.** At the time of the claimed invention seven of eight published clinical studies indicated a lack of effect of CLA on lowering blood lipids [reviewed in Larsen, T. M., Toubro, S., and Astrup, A. Efficacy and safety of dietary supplements containing CLA for the treatment of obesity: evidence from animal and human studies. *J Lipid Res* **2003**, *44*, 2234-41]. The authors also conclude, "the evidence from human, short-term studies suggest that CLA supplementation does not reduce body fat or increase fat-free mass. There is evidence that CLA isomers sold as dietary supplements have marked biological effects, but there is accumulating evidence that the CLA t10,c12 isomer may adversely influence human health by producing lipodystrophy and insulin resistance."

7.1.3. **Inoperability of CLA**. At the time of the claimed invention, the use of CLA in the described patient population would not have been expected to resulted in a decrease in plasma lipids or gain in subcutaneous fat due to previously disclosed prior art describing (1) no clinical effect of CLA on blood lipids in normal subjects, (2) the potential for the CLA to induce lipodystrophy and insulin resistance in humans, and (3) additional prior art describing the loss of adipose tissue, hepatomegaly, and development of lipodystrophy in mice administered CLA. Considering the prior art, one of ordinary skill would deem CLA to be of significant potential harm to the patient population.

7.1.4. **N-acetylcysteine (NAC) and antioxidants decrease insulin sensitivity and have no effect on blood lipids in the patient population.** Prior art also teaches that a 24-week antioxidant supplementation, including NAC increased fasting glucose, insulin and HOMA (homeostasis model assessment) scores reflecting an increased insulin resistance and had no effect on LDL, HDL or triglycerides in HIV-infected subjects with lipoatrophy[McComsey, G., Southwell, H., Gripshover, B., Salata, R., and Valdez, H. Effect

of antioxidants on glucose metabolism and plasma lipids in HIV-infected subjects with lipoatrophy. *J Acquir Immune Defic Syndr* **2003**, *33*, 605-7].

7.1.5. **Conclusion on the inoperability of the prior art**. Taken together these references indicate that the use of CLA or NAC in the disclosed patient population would be expected, by one of ordinary skill in the art, to be potentially harmful; and any beneficial effect of CLA either alone or in a combination with NAC in the patient population would be unexpected and provide a significant, unfulfilled need in the patient population.

7.2. *Evidence of unexpected clinical results*

7.2.1. At the time of filing the instant application, I was involved in a clinical trial to assess the effects of a formulation containing CLA and NAC on 16 HIV-1 subjects with hyperlipidemia and lipodystrophy who were receiving anti-retroviral medication (the claimed patient population).

7.2.2. This double-blinded, placebo-controlled, safety and efficacy pilot study in 16 male, HIV-1 subjects receiving HAART demonstrated that a formulation containing CLA and NAC was safe and well tolerated over twelve to 15 weeks.

7.2.3. The most dramatic and consistent effects of the CLA/NAC formulation were seen with serum lipid variables. Reduction of LDL cholesterol from 160 mg/dL at baseline was 20 percent within six weeks and 24 percent at twelve weeks. Additionally, the CLA/NAC formulation prevented the increase in triglycerides and attenuated the increase in triglyceride/HDL ratio seen in the placebo group.

7.2.4. With cholesterol-lowering medication, the CLA/NAC formulation appeared to complement efficacy, especially with the fibrate class of drugs.

7.2.5. Attenuation of HIV-1 viral replication by the CLA formulation was also observed

7.2.6. Further, in this short-term study the CLA/NAC formulation did not decrease insulin sensitivity or adversely affect body composition. Since both insulin sensitivity and visceral adipose tissue are strongly associated with the triglyceride/HDL ratio, however, it is likely that the CLA/NAC formulation would demonstrate a positive effect on insulin sensitivity and body composition in an appropriately longer clinical trial.

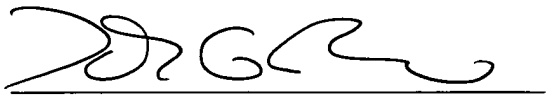
7.2.7. In view of the inoperability of the prior art, these results were unexpected and represent a significant finding on the combination of CLA and NAC in the claimed patient population.

8. ***Conclusion.*** It is obvious from the above disclosure of the prior art concerning the inoperability of CLA or NAC for decreasing blood lipids, increasing insulin sensitivity or increasing subcutaneous fat clinically describes a situation in which neither Factor A nor Factor B functions successfully. The instant disclosure that the combination of two nonfunctioning factors results in a successful result is an example of the synergistic, unexpected advantage of the claimed invention.

Oath

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 10/27/08



John G. Babish, Ph.D.
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Exhibit A

BIOGRAPHICAL SKETCH AND BIBLIOGRAPHY

John G. Babish — Chariperson, BIOnexus, Ltd.
Executive Vice President, Metaproteomics Inc.

Education

Institution and Location of Study	Degree	Date Conferred	Field
The Pennsylvania State University, State College, PA	B.S.	1968	Biochemistry
Cornell University, Ithaca, NY	M.S.	1974	Chemistry
Cornell University, Ithaca, NY	Ph.D.	1976	Biochemistry

Reseach and Professional Experience

Aug. 2002 – present — Consultant, Metaproteomics, Gig Harbor, WA. Metaproteomics develops clinically proven, patented dietary supplements and pharmaceuticals from natural sources. Duties include the design and evaluation of experiments elucidating mechanism of action and biological activity within complex mixtures.

1998 – present — (5% Effort) National Coordinator for the USDA Minor Species Drug Program (NRSP-7). The NRSP-7 program is funded by the USDA to provide funds and expertise necessary for the approval of pharmaceuticals used in the treatment of diseases associated with minor crop species. Duties include the coordination of industrial, academic and regulatory resources necessary for protocol development through final drug approval.

1997 – present — Co-founder and Chairperson of BIOnexus, Ltd. Ithaca, NY. BIOnexus develops and markets nutritional supplements to address health problems associated with AIDS. NutriVir™, the BIOnexus supplement for wasting in HIV/AIDS, generated approximately $600,000 in gross revenues in its first year of sales. NutriVir™ is reimbursed by Medicaid in 14 states.

1991 – 1996 — Founder, Chairperson, President and CEO of Paracelsian, Inc., Ithaca, NY. The Company was launched from the technology transfer program of Cornell University in 1991, and with the public offering in 1992 (Nasdaq,PRLN), became the first public corporation of a Cornell University technology transfer effort. Babish was associated with the attainment of over $12 million dollars in corporate financing.

1984 – 1996 — Tenured, Associate and Professor of Pharmacology and Toxicology, Department of Pharmacology, College of Veterinary Medicine, Cornell University. Offered the first course in molecular risk assessment in the USA in 1979; member of the graduate Fields of Pharmacology, Toxicology, Veterinary Medicine, Food Science and Epidemiology; successfully petitioned the State of New York for the

approval of the separate Fields of Toxicology and Pharmacology at Cornell University.

1978 – 1984 Assistant Professor, Department of Preventive Medicine, NYS College of Veterinary Medicine, Cornell University, Ithaca, NY.

1976 – 1978 Postdoctoral Scientist, Food and Drug Research Labs, Waverly, NY.

Invited Presentations (Recent of 38 presentations)

Micronutrient deficiencies in AIDS wasting at Progressive Management of AIDS Wasting: 2000. Hunter College, NYC. March 24, 2000.

Phytochemicals and NF-kB activation at IBC's Conference on The Health Benefits of Natural Phytoceuticals. Montreal Bonaventure Hilton, July 22 – 23, 1997.

Chemically-induced cell cycle stasis in immunotoxicology. 12th Annual NIOSH Conference on Mechanisms of Immunotoxicology – Role of Apoptosis in Immunotoxicology. University of West Virginia, Morgantown, WV. September 10 – 12, 1997.

Publications (Selected of 108 peer-reviewed publications)

Hall, A. J., Babish, J. G., Darland, G. K., Carroll, B. J., Konda, V. R., Lerman, R. H., Bland, J. S., and Tripp, M. L. Safety, efficacy and anti-inflammatory activity of rho iso-alpha-acids from hops. *Phytochemistry* **2008**, *69*, 1534-47.

Hall AJ, Tripp M, Howell T, Darland G, Bland JS, Babish JG. (2006) Gastric mucosal cell model for estimating relative gastrointestinal toxicity of non-steroidal anti-inflammatory drugs. *Prostaglandins Leukot Essent Fatty Acids.* 75(1):9-17.

Payne M.A., Babish J.G., Bulgin M., Lane M., Wetzlich S., Craigmill A.L. (2002) Serum pharmacokinetics and tissue and milk residues of oxytetracycline in goats following a single intramuscular injection of a long-acting preparation and milk residues following a single subcutaneous injection. J Vet Pharmacol Ther. 25(1):25-32.

Calabrese C., Berman S.H., Babish J.G., et al. (2000) A phase I trial of andrographolide in HIV positive patients and normal volunteers. Phytother Res. 14(5):333-338.

Ma,X., Stoffregen,D.A., Wheelock,G.D., Rininger,J.A. and Babish,J.G. (1997) Discordant hepatic expression of the cell division control enzyme p34cdc2 kinase, proliferating cell nuclear antigen, p53 tumor suppressor protein, and p21Waf1 cyclin-dependent kinase inhibitory protein after WY14,643 ([4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid) dosing to rats. Mol. Pharmacol., 51, 69-78.

Rininger,J.A., Goldsworthy,T.L. and Babish,J.G. (1997) Time course comparison of cell-cycle protein expression following partial hepatectomy and WY14,643-induced hepatic cell proliferation in F344 rats. Carcinogenesis, 18, 935-941.

Rininger,J.A., Stoffregen,D.A. and Babish,J.G. (1997) Murine hepatic p53, RB, and CDK inhibitory protein expression following acute 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure. Chemosphere, 34, 1557-1568.

Rininger,J.A., Wheelock,G.D., Ma,X. and Babish,J.G. (1996) Discordant expression of the cyclin-dependent kinases and cyclins in rat liver following acute administration of the hepatocarcinogen [4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio] acetic acid (WY14,643). Biochem. Pharmacol., 52, 1749-1755.

Vancutsem,P.M. and Babish,J.G. (1996) In vitro and in vivo study of the effects of enrofloxacin on hepatic cytochrome P-450. Potential for drug interactions. Vet. Hum. Toxicol., 38, 254-259.

Patents (Selected of 16 US and three foreign patents)

US Patent No. **7,279,185**	Curcuminoid compositions exhibiting synergistic inhibition of the expression and/or activity of cyclooxygenase-2.
US Patent No. **6,733,793**	Oral composition with insulin-like activities and methods of use.
US Patent No. **5,833,994**	Use of the Ah receptor and Ah receptor ligands to treat or prevent cytopathicity of viral infection.
US Patent No. **5,612,188**	Automated, multicompartmental cell culture system.
US Patent No. **5,529,899**	Immunoassay for Ah receptor transformed by dioxin-like compounds.
US Patent No. **5,496,703**	Indirect immunoassay for dioxin-like compounds